



# Identifying familial hypercholesterolemia in acute coronary syndrome

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## Purpose of review

Familial hypercholesterolemia is a frequent genetic disorder characterized by elevated LDL-cholesterol and premature coronary heart disease. Familial hypercholesterolemia remains largely underdiagnosed in the general population and for many patients the initial clinical manifestation is acute coronary syndromes (ACS). Furthermore, many missed diagnosis of familial hypercholesterolemia can also occur during hospitalization for ACS. In this review, we aim to discuss the identification and prognosis of familial hypercholesterolemia after hospitalization for ACS.

## Recent findings

The prevalence of familial hypercholesterolemia was about 10 times higher among patients hospitalized for ACS compared with the general population. Although 70% of patients with familial hypercholesterolemia were discharged with high-intensity statins, and 65% attended cardiac rehabilitation, less than 5% reached the recommended LDL-cholesterol target less than 1.8 mmol/l 1 year after ACS. Furthermore, patients with familial hypercholesterolemia and ACS were at high-risk of recurrence of cardiovascular events after discharge.

## Summary

A systematic screening strategy to identify patients with familial hypercholesterolemia at the time ACS is required to maximize secondary prevention and improve lipid management. It is expected that a substantial number of familial hypercholesterolemia patients would benefit from more effective lipid-lowering drugs after ACS, in addition to statins.

## Keywords

acute coronary syndrome, cardiovascular prevention, familial hypercholesterolemia, lipids, PCSK9

## INTRODUCTION

Familial hypercholesterolemia is the most prevalent genetic disease with an estimated prevalence of 1/200–1/500 in the general population. Familial hypercholesterolemia is characterized by elevated plasma levels of LDL-cholesterol (LDL-C) that can lead to premature coronary heart disease (CHD) if left untreated [1<sup>••</sup>,2<sup>••</sup>]. In the general population, familial hypercholesterolemia is underdiagnosed and undertreated, as less than 1% of familial hypercholesterolemia cases are managed adequately [3]. Early detection of familial hypercholesterolemia can reduce the cardiovascular risk, thanks to the use of lipid-lowering drugs such as statins [1<sup>••</sup>,4–6]. However, for many patients, the initial clinical manifestation of familial hypercholesterolemia is the occurrence of acute coronary syndromes (ACS) [7]. To improve the identification of patients with familial hypercholesterolemia, several clinical tools have been proposed by expert groups. Unfortunately, because of the lack of uniform strategy, the detection of familial hypercholesterolemia at time of ACS

is not systematically performed, although those patients are at a very high risk of recurrence of CHD events [8]. The timely review aims to summarize key issues on the identification of familial hypercholesterolemia in the ACS population.

## DEFINITIONS OF FAMILIAL HYPERCHOLESTEROLEMIA IN THE SETTING OF ACUTE CORONARY SYNDROMES

To improve the detection of familial hypercholesterolemia in the general population, several

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## KEY POINTS

- Familial hypercholesterolemia is the most prevalent genetic disease and is associated with premature CHD.
- The prevalence of familial hypercholesterolemia at time of hospitalization for acute coronary syndrome is 10 times higher than in the general population.
- Available clinical definitions can be used to diagnose familial hypercholesterolemia in patients with acute coronary syndromes.
- Patients with familial hypercholesterolemia have poorly controlled LDL-C levels 1 year after acute coronary syndromes despite statin treatment.
- After acute coronary syndrome, patients with familial hypercholesterolemia will be eligible for PCSK9 inhibitors in addition to high-dose statins.

diagnosis algorithms based on simple clinical criteria have been proposed. Although these algorithms have never been validated in cohorts of patients with ACS, they are useful and can be easily implemented in clinical practice for the management of ACS patients [9<sup>•</sup>]. The European Society of Cardiology (ESC), the European Society of Atherosclerosis, the National Lipid Association in the USA, and the International Familial Hypercholesterolemia foundation recommend the use of the Dutch Lipid Clinic Network algorithm to identify patients with familial hypercholesterolemia [10,11,12<sup>••</sup>]. The Dutch Lipid Clinic definition classifies patients in possible (3–5 points) and probable/definite familial hypercholesterolemia (>6 points) (Table 1). This algorithm takes into account LDL-C levels, clinical signs of lipid accumulation in the tissue, such as arcus lipoides or xanthomas, familial and personal history of premature CHD (<55 years for men; <60 years for women). For instance, a man without familial history of premature CHD or xanthomas, who presented with ACS at the age of 49 years with an LDL of 5.5 mmol/l will be classified a possible familial hypercholesterolemia (4 points). If the same patient has a LDL-C of 7 mmol/l, he will be classified as probable/definite familial hypercholesterolemia (7 points). In the UK, the National Institute for Health and Care Excellence guidelines recommend the use of the Simon Broome Register algorithm to identify patients with familial hypercholesterolemia, based on similar clinical criteria (Table 1) [13,14]. Very recently, the American Heart Association has further simplified the definition of clinical familial hypercholesterolemia by removing the use of arcus lipoides or xanthomas [15<sup>••</sup>].

If DNA testing is available, cascade screening of families may be performed using both a phenotypic and genotypic strategy [2<sup>••</sup>]. Nowadays, direct mutations have been identified for *LDLR*, *APOB*, and *PCSK9*. However, 60% of patients with familial hypercholesterolemia are mutation negative, which could decrease the efficiency of cascade screening, and a substantial proportion of them might have elevated LDL-C levels because of polygenic causes [16]. Among 231 patients with ACS younger than 50 years old in England, only three (1.3%) had LDLR mutation [17]. Thus, in the specific setting of ACS, the role of genetic testing for familial hypercholesterolemia has not been defined, and the impact of genetic mutations on the prognosis apart from phenotype is poorly known [18].

## PREVALENCE AND CHARACTERISTICS OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA AND ACUTE CORONARY SYNDROMES

The prevalence of familial hypercholesterolemia in the ACS population has been recently studied in Europe and Australia (Table 2) [9<sup>•</sup>,19<sup>•</sup>,20<sup>•</sup>,21]. The prevalence of familial hypercholesterolemia is considerably higher among patients hospitalized for ACS compared with the general population, from three to 20-fold higher. In the Swiss Special Program University Medicine - Acute Coronary (SPUM-ACS) cohort, including 4778 patients hospitalized for ACS, 1.6% [95% confidence interval (CI) 1.3–2.0%] fulfilled criteria of probable/definite familial hypercholesterolemia according to the Dutch Lipid Clinic definition [9<sup>•</sup>]. The prevalence was higher in 1451 ACS patients with premature CHD (<55 years old for men and <60 years old for women) reaching 4.8% for probable/definite familial hypercholesterolemias. In more than 7000 European patients with pre-existing CHD from the Euroaspire IV study, the prevalence of probable/definite familial hypercholesterolemia was 8.3%, reaching 15.4% among 2212 patients younger than 60 years old. In samples of 175 and 210 Australian patients with ACS younger than 60 years old, the prevalence of probable/definite familial hypercholesterolemia ranged from 1.5 to 14.3% according to the Dutch Lipid Clinic definition [20<sup>•</sup>,21].

The characteristics of ACS patients with clinical familial hypercholesterolemia were different from patients without familial hypercholesterolemia. By definition, they were younger and had higher proportion of personal or family history of premature CHD. Patients with familial hypercholesterolemia were more frequently smokers, but had less frequently diabetes or hypertension [9<sup>•</sup>,19<sup>•</sup>].

**Table 1.** Clinical definitions of familial hypercholesterolemia that can be used in acute coronary syndromes

|  | Grading                                |
|--|--|
| Dutch Lipid Clinic Network criteria  |  |
| First-degree relative with known premature atherosclerosis OR with known LDL-cholesterol >95th percentile, OR personal history of premature (<55 years men; <60 years women) cerebral or peripheral vascular disease, OR LDL-cholesterol 4.0–4.9 mmol/l <sup>a</sup>         | 1 point                                |
| Personal history of premature (<55 years men; <60 years women) CHD or first-degree relative with tendon xanthomata and/or arcus cornealis OR first-degree relative child below 18 years with LDL-cholesterol >95th percentile OR LDL-cholesterol 5.0–6.4 mmol/l <sup>a</sup> | 2 points                               |
| LDL-cholesterol 5.0–6.4 mmol/l <sup>a</sup>  | 3 points                               |
| Presence of arcus cornealis below 45 years   | 4 points                               |
| LDL-cholesterol 6.5–8.4 mmol/l <sup>a</sup>  | 5 points                               |
| Presence of tendon xanthomata  | 6 points                               |
| LDL-cholesterol >8.5 mmol/l <sup>a</sup> OR functional mutation in LDL receptor gene present   | 8 points                               |
| Possible familial hypercholesterolemia   | 3–5 points                             |
| Probable familial hypercholesterolemia   | 6–7 points                             |
| Definite familial hypercholesterolemia   | ≥8 points                              |
| Simon Broome Register criteria from NICE guidelines  |  |
| Total cholesterol >7.5 mmol/l OR LDL-cholesterol >4.9 mmol/l   |  |
| AND  |  |
| First-degree relative with known premature CHD (<55 years men; <60 years women)  | Possible familial hypercholesterolemia |
| Personal history of premature CHD (<55 years men; <60 years women)   | Possible familial hypercholesterolemia |
| Tendon xanthomas   | Definite familial hypercholesterolemia |
| DNA mutation   | Definite familial hypercholesterolemia |
| American Heart Association definition  |  |
| LDL-cholesterol >4.9 mmol/l  |  |
| AND  |  |
| First-degree relative with known premature CHD (<55 years men; <60 years women)  | Familial hypercholesterolemia          |
| First-degree relative with LDL-cholesterol >4.9 mmol/l   | Familial hypercholesterolemia          |

CHD, coronary heart disease; NA, not available; NICE, National Institute for Health and Care Excellence.

<sup>a</sup>Only in those with triglyceride levels <2.3 mmol/l.

**Table 2.** Prevalence of familial hypercholesterolemia according to the Dutch Lipid Clinic Network algorithm in different populations of patients with coronary heart disease

| Year | Population   | Prevalence of familial hypercholesterolemia   |
|------|--|---|
| 2012 | 210 patients with premature CHD in Australia   | Probable familial hypercholesterolemia 1.5%; possible familial hypercholesterolemia 24.0%           |
| 2015 | 175 patients with premature CHD in Australia   | Probable/definite familial hypercholesterolemia 14.3%; possible familial hypercholesterolemia 61.1% |
| 2015 | 7044 CHD patients from the EUROASPIRE IV registry in Europe                                  | Probable/definite familial hypercholesterolemia 8.3%; possible familial hypercholesterolemia 31.6%  |
| 2015 | 4778 patients with acute coronary syndrome, including 1451 with premature CHD in Switzerland | Probable/definite familial hypercholesterolemia 1.6%; possible familial hypercholesterolemia 17.8%  |

ACS, acute coronary syndromes; CHD, coronary heart disease; FH, familial hypercholesterolemia. Premature CHD is defined as ≤55 years for men and ≤60 years for women.

However, when examining only younger patients with premature CHD from the SPUM-ACS study, lower rates of diabetes, but similar rate of smoker and hypertension were found among familial hypercholesterolemia patients compared with patients without familial hypercholesterolemia (Fig. 1). In addition, higher levels of PCSK9 were associated with the diagnosis of familial hypercholesterolemia at the time of ACS [22]. However, whether PCSK9 might be an additional biomarker for detecting familial hypercholesterolemia on top of clinical and genetic criteria needs to be clarified [23].

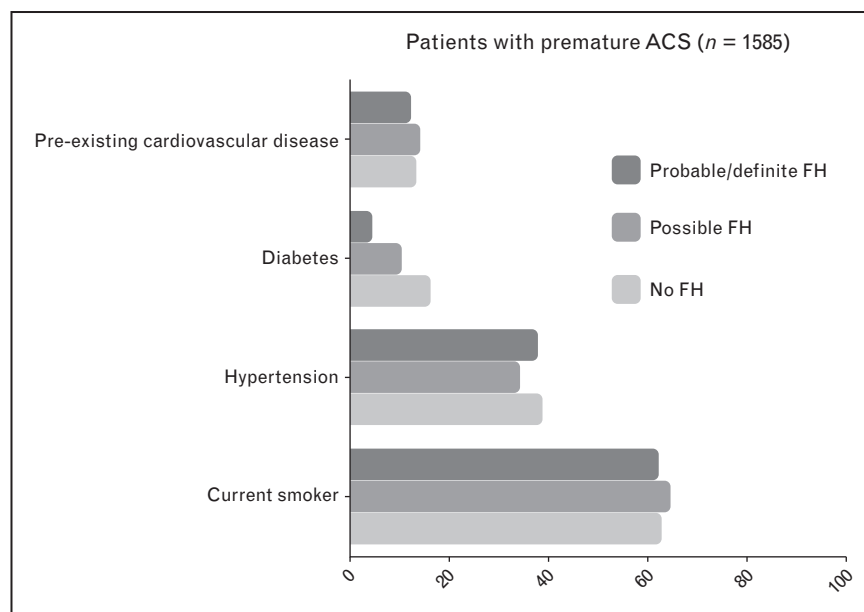
### QUALITY OF CARE OF FAMILIAL HYPERCHOLESTEROLEMIA IN PATIENTS WITH ACUTE CORONARY SYNDROMES

Observational data have shown that patients with familial hypercholesterolemia were undertreated before ACS, with only 40–70% of patients with familial hypercholesterolemia treated with statins prior ACS [9<sup>a</sup>,20<sup>a</sup>,24]. After hospitalization for ACS, guidelines recommend the prescription of high-dose statins, defined as atorvastatin 40 or 80 mg/day or rosuvastatin 20 or 40 mg/day, to maximize the reduction of LDL-C levels [25]. Large meta-analyses have shown that for each 1 mmol/l decrease in LDL-C levels, the relative risk of CHD events was reduced by 20%, but with larger absolute risk reduction among high-risk patients [26]. However, patients with familial hypercholesterolemia are not systematically treated with high-dose statins after hospital discharge for ACS. In 53 Australian

patients with familial hypercholesterolemia and ACS only 27% were discharged with high-dose statins in 2011 [21]. In the Swiss SPUM-ACS cohort, we found that 70% of the 78 ACS patients with probable/definite familial hypercholesterolemia were discharged with high-dose statins between 2009 and 2013 [9<sup>a</sup>].

The main reasons for nonprescription of high-dose statins in patients with familial hypercholesterolemia and ACS seemed to be statins intolerance, but data are still scarce on this issue [27]. Muscle symptoms associated with statins could have a huge impact on adherence, and it remains a frequent reason of statin discontinuation [28–30]. Lipid-lowering therapies were rarely intensified in the outpatient setting over the year after ACS, and in more than half of cases of statins interruption, patients reported a shared decision with their physicians [30]. One year after their ACS, 65% of patients with familial hypercholesterolemia were still on high-dose statins [9<sup>a</sup>]. Additional nonstatin lipid-lowering therapies (e.g. fibrates, ezetimibe, niacin, or resins) were uncommonly prescribed [31]. This may change with the recent release of ESC guidelines for the management of ACS that now recommends the additional use of nonstatin agents for patients who had LDL-C levels more than 1.8 mmol/l [32].

Among 78 patients with ACS and probable/definite familial hypercholesterolemia in the Swiss SPUM-ACS cohort, only two reached the recommended target less than 1.8 mmol/l 1 year after ACS [9<sup>a</sup>]. Besides lipid-lowering therapies, attendance



**FIGURE 1.** Prevalence of major cardiovascular risk factors in patients with FH and premature ACS, definition of FH was based on the Dutch Lipid Clinic algorithm. ACS, acute coronary syndrome; FH, familial hypercholesterolemia.

to cardiac rehabilitation was also shown to improve control of LDL-C [31]. We reported that only 65% of 78 patients with probable/definite familial hypercholesterolemia attended cardiac rehabilitation after ACS [9<sup>o</sup>]. These data not only confirm that available therapies are not sufficient to reach the recommended LDL-C target of less than 1.8 mmol/l in ACS patients with familial hypercholesterolemia, but that room for improvement exists in the secondary prevention of familial hypercholesterolemia after hospital discharge.

### PROGNOSIS OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA AND ACUTE CORONARY SYNDROMES

Several observational studies conducted in lipid clinics have examined the cardiovascular prognosis of patients with familial hypercholesterolemia, but the recurrence risk of coronary events after a first ACS has been poorly studied in patients with familial hypercholesterolemia. The Simon Broome Register Group examined the prognosis over a 14-year period of more than 1800 patients with definite familial hypercholesterolemia and more than 1500 patients with possible familial hypercholesterolemia included from 1980 to 2006 [8,33]. Among them about 30% of men and 20% of women had history of CHD at the beginning of follow-up. The authors could confirm the beneficial effects of statins in patients with familial hypercholesterolemia, both in primary and secondary prevention, showing the importance of early identification of familial hypercholesterolemia [8]. In a retrospective cohort study among patients from Dutch Lipid clinics, the cardiovascular prognosis associated with genotype and phenotype of familial hypercholesterolemia could be assessed [34]. Patients with familial hypercholesterolemia who had pathogenic LDLR mutations with elevated LDL-C levels presented higher risk of CHD events, compared with patients without mutations and lower LDL-C levels (hazard ratio 3.64, 95% CI 3.24–4.08,  $P < 0.001$ ) [35]. However, only 7% of the study population had pre-existing CHD, and these results may not be extrapolated to patients with familial hypercholesterolemia and ACS. In another Dutch lipid clinic of 131 patients with familial hypercholesterolemia and CHD and 214 patients with familial hypercholesterolemia without CHD, the risk of coronary events was seven-fold higher in secondary prevention than in primary prevention [36].

These results suggest an increased risk of recurrence of CHD events in patients with familial hypercholesterolemia after a first ACS that can be

significantly improved with statins [5]. However, more data are needed in secondary prevention of patients with familial hypercholesterolemia, as the prognosis after ACS has been poorly addressed, particularly after prescription of high-dose statins. The high residual cardiovascular risk of patients with familial hypercholesterolemia after ACS despite use of high-intensity statins may need intensification of secondary prevention and lipid management.

### PCSK9 INHIBITORS FOR PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA AND ACUTE CORONARY SYNDROMES

Clinical trials have shown that PCSK9 inhibitors added to maximally tolerated statin doses can further decrease LDL-C by up to 60% [37,38]. PCSK9 clinical trials have mainly enrolled patients who had poorly controlled LDL-C despite maximally tolerated statin dose, including patients with familial hypercholesterolemia [37]. The Food and Drug Administration and European medicines agency approved the use of PCSK9 inhibitors in patients with familial hypercholesterolemia if optimal LDL-C levels could not be reached despite maximally tolerated statin dose or in case of intolerance to statins (Table 3) [39]. A recent publication of the US National Lipid Association made some recommendations regarding the eligibility for the treatment with PCSK9 inhibitors in secondary prevention: LDL-C more than 100 mg/dl while on maximally tolerated statin ( $\pm$ ezetimibe); high-risk patients with recurrent events and LDL-C more than 70 mg/dl; intolerance to statin therapy or statin-associated muscle symptoms [40]. Based on these criteria, it is expected that a substantial number of patients with familial hypercholesterolemia would be eligible for PCSK9 inhibitors after ACS.

A recent meta-analysis reviewing the effects of PCSK9 in adults with hypercholesterolemia reported a reduction in cardiovascular mortality by 55% (odds ratio 0.45, 95% CI 0.23–0.86,  $P = 0.015$ ), although currently the number of reported CVD deaths was small [41]. Two trials [Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab Long-Term; Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER-1) and (OSLER-2)] have shown in post-hoc analysis a reduction in major adverse cardiovascular events of 50% in the PCSK9 inhibitors group among high-risk patients, such as patients with familial hypercholesterolemia and ACS [42,43]. Thus, new lipid-lowering therapies (e.g. PCSK9 inhibitors) may be recommended for patients at high-risk



**Table 3.** Indications for the use of PCSK9 inhibitors according to regulatory agencies

| Alirocumab (Praluent)  | Evolocumab (Repatha)   |
|--|--|
| European Medicines Agency  |  |
| Primary hypercholesterolemia (familial heterozygous or nonfamilial) or mixed dyslipidaemia in addition to lifestyle counselling:                 | Adults with primary hypercholesterolemia (familial heterozygous or nonfamilial) or mixed dyslipidaemia in addition to lifestyle counselling:                 |
| In combination with maximally tolerated statin or (statin + ezetimibe) in patients who did not reach the LDL-cholesterol targets                 | In combination with maximally tolerated statin or (statin + ezetimibe) in patients who did not reach the LDL-cholesterol targets                             |
| In monotherapy or in combination with nonstatin agent in patients with intolerance or contra-indications to statin                               | In monotherapy or in combination with nonstatin agent in patients with intolerance or contra-indications to statin   |
|  | Adults with familial homozygous hypercholesterolemia in combination with other lipid-lowering agents (statin and nonstatin)                                  |
| Effects on morbidity and mortality are still under investigations  | Effects on morbidity and mortality are still under investigations  |
| Food and Drug Administration   |  |
| Adults with familial heterozygous hypercholesterolemia in addition to lifestyle counselling and in combination with maximally tolerated statin   | Adults with familial heterozygous or homozygous hypercholesterolemia in addition to lifestyle counselling and in combination with maximally tolerated statin |
| Adults with clinical cardiovascular disease (e.g. myocardial infarction or cerebrovascular disease) who need additional LDL-cholesterol lowering | Adults with clinical cardiovascular disease (e.g. myocardial infarction or cerebrovascular disease) who need additional LDL-cholesterol lowering             |

of CHD events such as patients with familial hypercholesterolemia and ACS, as those patients frequently present with poorly controlled LDL-C levels despite high-dose statins and ezetimibe [44,45]. The 2016 ESC prevention guidelines will be published shortly after this review and will hopefully provide guidance on the eligibility for the use of PCSK9 inhibitors in clinical practice, as well as the LDL-C targets to achieve in patients with familial hypercholesterolemia and ACS.

### GAPS IN EVIDENCE AND NEEDS FOR THE FUTURE

Should we consider patients with familial hypercholesterolemia as a homogenous group of patients with similar risk of recurrence after ACS? Available data suggest that PCSK9 levels are not associated with an increased risk of recurrence after ACS, and may not be useful to identify patients with familial hypercholesterolemia at higher risk of recurrence [22]. A homogenous screening strategy for the diagnosis of familial hypercholesterolemia after ACS needs to be implemented, and further researches are needed to clarify the optimal lipid-lowering treatment for those patients. In addition, the cost-effectiveness of screening strategies and PCSK9 inhibitors needs to be specifically studied in patients with familial hypercholesterolemia and ACS [46].

### CONCLUSION

The lack of systematic identification of familial hypercholesterolemia in patients with ACS is an important gap in quality of care that need to be addressed, as the prevalence of familial hypercholesterolemia in ACS patients is dramatically higher than in the general population. There is major room to improve the control of LDL-C among patients with familial hypercholesterolemia after ACS, by intensifying statin treatment and secondary prevention intervention. Furthermore, as patients with familial hypercholesterolemia are at very high-risk of recurrence after first ACS despite current treatment, the use of PCSK9 inhibitors in these patients may have large health benefits.

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### Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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